Claims 1, 21 and 45 have been amended. Claim 1 has been amended to specify a process for preparing a thermosensitive nanoporous polymer. Claim 21 has been similarly amended to specify that the thermosensitive polymer is nanoporous. Claim 45 has been amended in form only, for clarity.

The Written Opinion indicates that claims 1-4, 21-31 and 45 lack novelty and inventive step, having regard to the 12 cited references. Applicant respectfully submits that the claims, as amended, are novel and inventive, for the following reasons.

The International Search Report indicates that references US 5,399,618; EP 217485; US 5,296,627; US 5,721,313; US 5,294,692; US 4,806,609; and US 5,874,495 are relevant to various of claims 1 to 4 of the instant application and that WO 97/05185; US 5,410,016; US 2002/0187182; US 2002/0120015; and US 5,587,143 are relevant to various of claims 21 to 31 and 45 of the instant application. Claim 1 as amended is directed to a process for preparing a nanoporous thermosensitive polymer comprising polymerizing a microemulsion including a monomer capable of forming a thermosensitive polymer and a polymerizable surfactant. Independent claims 21, 22 and 26 are directed to various methods employing a thermosensitive polymer that is nanoporous, such as dressing and undressing a wound, delivering a therapeutic agent to a wound, and delivering a cell to a graft site. Independent claims 29, 30 and 31 are directed to a thermosensitive polymer that is nanoporous. None of the cited references teach or suggest polymerizing a microemulsion of a monomer capable of forming a thermosensitive polymer and a polymerizable surfactant. Such a process of forming the polymer results in a polymer that is nanoporous. Furthermore, none of the cited references otherwise teach or suggest a thermosensitive polymer that is nanoporous.

A nanoporous polymer is formed using microemulsion polymerization techniques to polymerize a monomer together with a polymerizable surfactant. US 5,399,618 describes polymer emulsions useful for thickening aqueous solutions. These polymers are formed using emulsifiers appropriate for emulsifying the monomers and for maintaining the polymer in a dispersed condition. This reference does not disclose the use of polymerizable surfactants, and thus the disclosed polymers are not nanoporous. Similarly, the polymers disclosed in US 5,721,313 are formed using a non-polymerizable surfactant and are not nanoporous.

US 5,296,627 describes surfactants for use in emulsion polymerization of ethylenically unsaturated monomers. Example 14 of this cited reference describes use of a particular described surfactant in polymerizing monomers from a standard emulsion. However, this reference does not disclose polymerization of a microemulsion to polymerize a monomer capable of forming a thermosensitive polymer and a polymerizable surfactant, with the end result of a thermosensitive polymer that is nanoporous. Similarly, EP 217485 describes a copolymer formed from polymerizing a certain class of polymerizable surfactant and ethylenically unsaturated monomers, using standard emulsion techniques, but does not describe the use of microemulsion techniques to form a nanoporous thermosensitive polymer. US 5,294,692 describes polymers of novel monomers, and which can include comonomers of acrylamide and methacrylamide. This reference also does not disclose the use of microemulsion techniques to form a nanoporous thermosensitive polymer.

The present application indicates that such monomers are capable of forming a polymer having a lower critical solution temperature and undergoing a phase shift to become dehydrated above this temperature and hydrated below this temperature. Such monomers include acrylamide derivatives, including alkylated acrylamides. US 4,806,609 and US 5,874,495 do not disclose the use of monomers which are capable of forming a thermosensitive polymer, or the copolymerization of such a monomer with a polymerizable surfactant to form a thermosensitive nanoporous polymer.

Thus, none of the above cited references disclose the process of preparing a thermosensitive nanoporous polymer by polymerizing a microemulsion including a monomer capable of forming a thermosensitive polymer and a polymerizable surfactant. Furthermore, none of the above cited references, alone or in combination, suggest such a process for producing a nanoporous thermosensitive polymer. Claims 1 to 20 of the present application are thus novel and inventive in light of these references.

WO 97/05185 describes thermosensitive macromers which are synthesized by conventional aqueous polymerization and crosslinking techniques. The macromers are used to form a gel in aqueous solution which may be crosslinked while in gel form. Since the crosslinking is performed in aqueous solution using standard methods, the resulting gel is not nanoporous. The polymer is not formed from a microemulsion.

US 5,410,016 describes hydrogels of polymerized and crosslinked macromers, polymerized using conventional photopolymerization. The described hydrogels are not formed by polymerizing a monomer with a polymerizable surfactant in a microemulsion and thus are not nanoporous.

US 2002/0187182 describes a cross-linked polymer fleece, which is water-absorbent, and is discloses that the fleece is formed to be macroporous or microporous. The claims of the present invention relate to nanoporous thermosensitive polymers, which this reference does not teach or suggest.

US 2002/0120015 describes a microemulsion delivery system that is useful for delivery of drugs which are not soluble or not fully soluble in water. The microemulsion comprises a polymer formed using conventional polymerization methods, but the microemulsion is formed by mixing of components, including the polymer, and is not subsequently polymerized to form a nanoporous structure. Thus, this reference does not teach the use of a nanoporous thermosensitive polymer.

US 5,587,143 relates to milled nanoparticles comprising a surfactant which is absorbed on the surface of the particles, but is not reacted with the particles, in order to facilitate milling. The surfactant is a block copolymer of ethylene oxide and butylene oxide. The reference does not teach or disclose a thermosensitive nanoporous polymer or use for such a polymer.

Thus, the aforementioned references WO 97/05185; US 5,410,016; US 2002/0187182; US 2002/0120015; and US 5,587,143 do not teach or suggest the formation of a thermosensitive nanoporous polymer, or the use of such a polymer in biomedical applications such as those claimed in claims 21, 22 and 26 of the present application. Therefore, claims 21 to 31 and 45 are novel and inventive in light of these references.

Favourable reconsideration is therefore respectfully requested.

No new matter has been added by this amendment.

Respectfully submitted,

Ms. Audrey Yap

YU SARN AUDREY & PARTNERS
190 Middle Road, #12-04
Singapore 188979

Telephone: (65) 6358-2865
Facsimile: (65) 6358-2864

February 17, 2005
93231-37 (SAH/kep)

WHAT IS CLAIMED IS:

1. A process for preparing a thermosensitive nanoporous polymer comprising polymerizing a microemulsion comprising a first monomer that is capable of forming a thermosensitive polymer and a polymerizable surfactant.

2. The process of claim 1 wherein the first monomer is an acrylamide derivative.

3. The process of claim 2 wherein the first monomer is an alkylated acrylamide.

4. The process of claim 3 wherein the first monomer is *N*-isopropylacrylamide.

5. The process of claim 4 wherein the polymerizable surfactant is ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate or fluronic68-diacrylate.

6. The process of claim 5 wherein the microemulsion comprises a comonomer.

7. The process of claim 6 wherein the microemulsion comprises methyl methacrylate or 2-hydroxyethyl methacrylate.

8. The process of claim 7, wherein the polymerizable surfactant is ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate and the microemulsion further comprises a chemical cross-linker.

9. The process of claim 8, wherein the cross-linker is EGDMA.

10. The process of claim 9, wherein the microemulsion further comprises a photo-initiator.

11. The process of claim 10, wherein the photo-initiator is 2,2-dimethoxy-2-phenylacetophenone.

12. The process of claim 11, wherein the polymerizing comprises subjecting the microemulsion to ultraviolet radiation.

Replacement Page
18 February 2005

13. The process of claim 12 comprising the step of preparing a layer of microemulsion of a desired thickness prior to polymerization.

14. The process of claim 13, wherein the microemulsion comprises about 20 % (w/w) *N*-isopropylacrylamide, about 10% (w/w) methyl methacrylate, about 10 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

15. The process of claim 13, wherein the microemulsion comprises about 10 % (w/w) *N*-isopropylacrylamide, about 10% (w/w) methyl methacrylate, about 20 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

16. The process of claim 13, wherein the microemulsion comprises about 7.5 % (w/w) *N*-isopropylacrylamide, about 7.5 % (w/w) methyl methacrylate, about 15 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 33% (w/w) water and about 2% ethylene glycol dimethacrylate.

17. The process of claim 13, wherein the microemulsion comprises about 10 % (w/w) *N*-isopropylacrylamide, about 20 % (w/w) methyl methacrylate, about 10 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

18. The process of claim 13, wherein the microemulsion comprises about 25 % (w/w) *N*-isopropylacrylamide, about 10 % (w/w) methyl methacrylate, about 5 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

19. The process of claim 13, wherein the microemulsion comprises about 30 % (w/w) *N*-isopropylacrylamide, about 10 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w)

water and about 2% ethylene glycol dimethacrylate.

20. The process of claim 13, wherein the microemulsion comprises about 10 % (w/w) *N*-isopropylacrylamide, about 25 % (w/w) methyl methacrylate, about 5 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

21. A method of dressing and undressing a wound comprising:

applying a thermosensitive nanoporous polymer to a wound;

immediately prior to removing the polymer from the wound, reducing the temperature of thermosensitive nanoporous polymer to facilitate removal of the polymer; and

removing the thermosensitive nanoporous polymer from the wound.

22. A method of delivering a therapeutic agent to a wound comprising:

incorporating a therapeutic agent into a thermosensitive nanoporous polymer; and

applying the thermosensitive nanoporous polymer to the wound.

23. The method of claim 22, wherein the therapeutic agent is a drug, an antibiotic, an anti-inflammatory agent, a clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, or a ligand for a cell surface receptor.

24. The method of claim 22, wherein the therapeutic agent is a drug or an antibiotic.

25. The method of claim 22, wherein the therapeutic agent is a wound healing accelerator.

26. A method of delivering a cell to a graft site comprising:

culturing the cell on a thermosensitive nanoporous polymer; and

placing the polymer comprising the cell onto the graft site.

27. The method of claim 26, further comprising:

reducing the temperature of the thermosensitive nanoporous polymer to facilitate removal of the polymer; and

removing the polymer from the graft site.

28. The method of claim 27, wherein the step of reducing the temperature is performed after placing the thermosensitive nanoporous polymer carrying the cell onto the graft site.

29. A thermosensitive nanoporous polymer when prepared by the process of any one of claims 1 to 20.

30. A thermosensitive nanoporous membrane when prepared by the process of claim 13.

31. A thermosensitive polymer which is nanoporous.

32. The thermosensitive nanoporous polymer of claim 31 having a decomposition temperature of at least about 300°C.

33. The thermosensitive nanoporous polymer of claim 32 having a water vapour transmission rate of about 500 to about 2000 $g/m^2/day$.

34. The thermosensitive nanoporous polymer of claim 33 having a tensile strength of about 4 to about 20 MPa.

35. The thermosensitive polymer of claim 34 formed from a microemulsion comprising a first monomer capable of forming a thermosensitive polymer and a polymerizable surfactant.

36. The thermosensitive nanoporous polymer of claim 35 wherein the first monomer

is *N*-isopropylacrylamide.

37. The thermosensitive nanoporous polymer of claim 36 wherein the polymerizable surfactant is ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate or fluronic68-diacrylate.

38. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 20:10:10:35:23:2.

39. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 10:10:20:35:23:2.

40. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 7.5:7.5:15:35:33:2.

41. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 10:20:10:35:23:2.

42. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 25:10:5:35:23:2.

43. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion

comprises *N*-isopropylacrylamide, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 30:10:35:23:2.

44. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 10:25:5:35:23:2.

45. The method of claim 28 wherein the graft site is a round window membrane of an ear, or a cornea, of a subject.

WHAT IS CLAIMED IS:

1. A process for preparing a thermosensitive nanoporous polymer comprising polymerizing a microemulsion comprising a first monomer that is capable of forming a thermosensitive polymer and a polymerizable surfactant.

2. The process of claim 1 wherein the first monomer is an acrylamide derivative.

3. The process of claim 2 wherein the first monomer is an alkylated acrylamide.

4. The process of claim 3 wherein the first monomer is *N*-isopropylacrylamide.

5. The process of claim 4 wherein the polymerizable surfactant is ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate or fluronic68-diacrylate.

6. The process of claim 5 wherein the microemulsion comprises a comonomer.

7. The process of claim 6 wherein the microemulsion comprises methyl methacrylate or 2-hydroxyethyl methacrylate.

8. The process of claim 7, wherein the polymerizable surfactant is ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate and the microemulsion further comprises a chemical cross-linker.

9. The process of claim 8, wherein the cross-linker is EGDMA.

10. The process of claim 9, wherein the microemulsion further comprises a photo-initiator.

11. The process of claim 10, wherein the photo-initiator is 2,2-dimethoxy-2-phenylacetophenone.

12. The process of claim 11, wherein the polymerizing comprises subjecting the microemulsion to ultraviolet radiation.

13. The process of claim 12 comprising the step of preparing a layer of microemulsion of a desired thickness prior to polymerization.

14. The process of claim 13, wherein the microemulsion comprises about 20 % (w/w) *N*-isopropylacrylamide, about 10% (w/w) methyl methacrylate, about 10 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

15. The process of claim 13, wherein the microemulsion comprises about 10 % (w/w) *N*-isopropylacrylamide, about 10% (w/w) methyl methacrylate, about 20 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

16. The process of claim 13, wherein the microemulsion comprises about 7.5 % (w/w) *N*-isopropylacrylamide, about 7.5 % (w/w) methyl methacrylate, about 15 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 33% (w/w) water and about 2% ethylene glycol dimethacrylate.

17. The process of claim 13, wherein the microemulsion comprises about 10 % (w/w) *N*-isopropylacrylamide, about 20 % (w/w) methyl methacrylate, about 10 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

18. The process of claim 13, wherein the microemulsion comprises about 25 % (w/w) *N*-isopropylacrylamide, about 10 % (w/w) methyl methacrylate, about 5 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

19. The process of claim 13, wherein the microemulsion comprises about 30 % (w/w) *N*-isopropylacrylamide, about 10 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w)

water and about 2% ethylene glycol dimethacrylate.

20. The process of claim 13, wherein the microemulsion comprises about 10 % (w/w) *N*-isopropylacrylamide, about 25 % (w/w) methyl methacrylate, about 5 % (w/w) 2-hydroxyethyl methacrylate, about 35 % (w/w) ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, about 23% (w/w) water and about 2% ethylene glycol dimethacrylate.

21. A method of dressing and undressing a wound comprising:

applying a thermosensitive nanoporous polymer to a wound;

immediately prior to removing the polymer from the wound, reducing the temperature of thermosensitive nanoporous polymer to facilitate removal of the polymer; and

removing the thermosensitive nanoporous polymer from the wound.

22. A method of delivering a therapeutic agent to a wound comprising:

incorporating a therapeutic agent into a thermosensitive nanoporous polymer; and

applying the thermosensitive nanoporous polymer to the wound.

23. The method of claim 22, wherein the therapeutic agent is a drug, an antibiotic, an anti-inflammatory agent, a clotting factor, a hormone, a nucleic acid, a peptide, a cellular factor, or a ligand for a cell surface receptor.

24. The method of claim 22, wherein the therapeutic agent is a drug or an antibiotic.

25. The method of claim 22, wherein the therapeutic agent is a wound healing accelerator.

26. A method of delivering a cell to a graft site comprising:

culturing the cell on a thermosensitive nanoporous polymer; and

placing the polymer comprising the cell onto the graft site.

27. The method of claim 26, further comprising:

reducing the temperature of the thermosensitive nanoporous polymer to facilitate removal of the polymer; and

removing the polymer from the graft site.

28. The method of claim 27, wherein the step of reducing the temperature is performed after placing the thermosensitive nanoporous polymer carrying the cell onto the graft site.

29. A thermosensitive nanoporous polymer when prepared by the process of any one of claims 1 to 20.

30. A thermosensitive nanoporous membrane when prepared by the process of claim 13.

31. A thermosensitive polymer which is nanoporous.

32. The thermosensitive nanoporous polymer of claim 31 having a decomposition temperature of at least about 300°C.

33. The thermosensitive nanoporous polymer of claim 32 having a water vapour transmission rate of about 500 to about 2000 $g/m^2/day$.

34. The thermosensitive nanoporous polymer of claim 33 having a tensile strength of about 4 to about 20 MPa.

35. The thermosensitive polymer of claim 34 formed from a microemulsion comprising a first monomer capable of forming a thermosensitive polymer and a polymerizable surfactant.

36. The thermosensitive nanoporous polymer of claim 35 wherein the first monomer

is *N*-isopropylacrylamide.

37. The thermosensitive nanoporous polymer of claim 36 wherein the polymerizable surfactant is ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate or fluronic68-diacrylate.

38. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 20:10:10:35:23:2.

39. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 10:10:20:35:23:2.

40. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 7.5:7.5:15:35:33:2.

41. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 10:20:10:35:23:2.

42. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 25:10:5:35:23:2.

43. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion

comprises *N*-isopropylacrylamide, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 30:10:35:23:2.

44. The thermosensitive nanoporous polymer of claim 37, wherein the microemulsion comprises *N*-isopropylacrylamide, methyl methacrylate, 2-hydroxyethyl methacrylate, ω-methoxy poly(ethylene oxide)$_{40}$ undecyl α-methacrylate, water and ethylene glycol dimethacrylate in a ratio of approximately 10:25:5:35:23:2.

45. The method of claim 28 wherein the graft site is ~~the~~ a round window membrane of the ear of a subject or cornea.